An Industry View of FIH Studies: What do we get right and where can we improve?

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Author Disclosures and Disclaimer

- **Sarah Robertson is an employee of Vertex Pharmaceuticals Incorporated and may own stock or options in that company**

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Hindsight 20/20

WHAT DO GET RIGHT?

Safety comes first

- ✓ Risk-based approaches to FIH, not one-size-fits all
- ✓ Protocols with clear, well-defined dose escalation and stopping criteria on the basis of emerging PK and safety
- ✓ Strong safety record defining starting doses based on ICH M3(R2)
- ✓ Sentinel subject dosing, where appropriate

Strong partnership with CRO

- ✓ **PI is well-informed of investigational agent and risks**
  - Early review of the IB
  - PI and staff provide input on draft protocol
  - Frank and open communication of anticipated risks
- ✓ **Protocol training, site initiation visits and a LOT of preplanning**
- ✓ **Clearly documented roles and responsibilities for decision-making**
- ✓ **Candid and frequent dialogue between Sponsor Medical Monitor and PI**

Smart study design & conduct

- ✓ Multi-part studies allow for safe yet expedient development
- ✓ Innovation in data reporting/analysis + modern bioanalytical methods ensure safe and efficient dose escalation and study progression
- ✓ Maximize dose escalation in controlled Phase 1 setting to allow for safe dose-ranging in patients in Phase 2

WHAT CAN WE DO BETTER?

Technology

More timely and interactive review of safety data for the Sponsor

More efficient data collection, cleaning, and reporting

Biomarkers

Identification of therapeutic target and dose escalation based on PD endpoints, not just PK

Modeling

Better use of PBPK and other innovative modeling approaches for clinical PK predictions (moving beyond allometric scaling)

Modeling approaches for dose escalation decisions, accounting for variability/outliers

Subjects

Better integration of women in FIH

Earlier exploration of safety, PK, and PD in limited patient cohorts as part of FIH


Foresight 20/20